Hogan Lovells

There'll Be Some Changes Made: President Signs Prescription Drug and Biologic User Fee Reauthorization Act

21 August 2017

On August 18, 2017, President Trump signed into law the FDA Reauthorization Act (FDARA). FDARA reauthorizes user fees paid to FDA to support regulatory review of innovator drugs and biologics, medical devices, generic drugs, and biosimilar biologics. The fees fund FDA's review of premarket approval applications, and related regulatory activities, for new medical products. In exchange, the Agency agrees to meet certain goals negotiated with industry representatives. The negotiated goals are listed in separate FDA documents that are incorporated into the statute by reference. On top of the user fee program changes agreed to by the Agency and industry, Congress introduced numerous provisions affecting the Agency. Our summary below highlights the most significant provisions relating to pharmaceuticals and biotechnology products.

I. Priority Approval and Exclusivity for Generic Drugs

Priority review of generic drugs with pre-submission facility correspondence. Section 801 of FDARA establishes a priority review category for abbreviated new drug applications (ANDAs) under which FDA will review and act upon qualifying ANDA submissions within 8 months. To qualify, an application must be for a drug for which there are no more than three approved drugs listed in the Orange Book and for which there are no blocking patents and exclusivities, or the drug is on the list of drug shortages under FDCA 506E. In addition, the applicant is required to provide pre-submission facility correspondence to FDA at least 60 days prior to submission of the ANDA. The correspondence must provide complete and accurate information on facilities involved in manufacturing and testing of the drug so as to enable FDA to determine whether facility inspections are necessary. This past June, FDA released a draft Guidance for Industry titled ANDAs: Pre-Submission Facility Correspondence Associated with Priority Submissions that provided recommendations on the content and format of pre-submission facility correspondence.

180-day exclusivity for competitive generic therapies. Section 803 of FDARA creates a designation process for "competitive generic therapies" to expedite the development and review of qualifying ANDAs. FDA will designate a drug as a competitive generic therapy if there is "inadequate generic competition," meaning there is no more than one drug that is listed in the Orange Book either as the reference listed drug (RLD) or a generic product with the same RLD as the drug for which designation is being sought. An applicant may request designation as a competitive generic therapy at any time prior to, or concurrent with, submission of an ANDA. To incentivize the development of competitive generic therapies, section 808 of FDARA creates a 180-

day exclusivity period for the first approved applicant for a drug that is designated as a competitive generic therapy and for which there are no unexpired patents or exclusivities listed with the RLD.

Expanded scope of drug applications that may be approved when protected pediatric information is omitted from labeling. Section 505A(o) of the Food, Drug, and Cosmetic Act (FDCA) prohibits FDA from withholding approval of an abbreviated new drug application (ANDA) because the ANDA omits a pediatric indication or other aspect of labeling of the reference listed drug (RLD) that is protected by a patent or three-year exclusivity. In addition, 505A(o) authorizes FDA to include in the ANDA labeling any warnings, precautions or contraindications that the Agency considers appropriate as well as a statement that the drug is not approved for the pediatric indication due to marketing exclusivity. Section 608 of FDARA expands the scope of FDCA 505A(o) to include 505(b)(2) applications in addition to ANDAs, such that 505(b)(2) applications cannot be denied approval in the basis that its labeling omits a pediatric indication or other aspect of labeling that is protected by the RLD holder's patent or exclusivity. As with ANDAs, FDA may require a statement in the 505(b)(2) labeling that the drug is not approved for the pediatric indication due to marketing exclusivity in addition to any appropriate safety information. Section 608 also expands the description of relevant exclusivities to include orphan drug exclusivity, pediatric exclusivity and qualified infectious disease product exclusivity.

II. Changes in the Fee Funding Structure

Previously, user fees for drugs have been structured to derive one-third of the total revenue from application fees, one-third from drug manufacturing establishments, and one-third from annual fees assessed on approved products. Section 102 of the new law alters the allocation so that 20% of revenue will be derived from one-time application fees and 80% of revenue will be derived from an annual "program fee" that is assessed on the application holder of each approved drug product. At a Congressional hearing on the bill, Janet Woodcock, Director of CDER, testified that this change was made to increase reliance on annual fees and decrease reliance on one-time fees in order to allow FDA a more predictable revenue stream.

Although the balance was selected to minimize disruption in the overall amount of fees paid, some companies may find their fees change in the wake of this adjustment. For example, companies that have many approved drugs but plan to submit few, if any, applications in the coming five years will see a higher fee burden than they would have faced under the old funding scheme. Conversely, companies with few approved products that plan to submit several applications will see lower overall fees, as FDA relies more heavily on annual fees and less on application fees.

III. Patient Experience and Real World Evidence

Patient Experience Data. Section 605 of FDARA amends section 569C of the FDCA (21 USC 360bbb-8c), which was significantly amended under the 21st Century Cures Act. Section 569C directs FDA to engage the views of patients in the medical product development and approval phases and to publish a statement following the approval of a New Drug Applications (NDA) or a Biologics License Application (BLA) that describes the patient experience data, if any, submitted and reviewed as part of the application. Section 605 of FDARA expands the types of patient experience data to be considered and discussed in the statement. Previously, FDCA 569C called for reporting patient experience data on "the impact of such disease or condition, or a related therapy, on patients' lives." 21 USC 360bbb-8c(c)(2)(A). As amended, the provision calls for data on "the

impact (*including physical and psychosocial impacts*) of such disease or condition, or a related therapy *or clinical investigation*, on patients' lives."

The change appears to clarify, or possibly expand, the scope of data that FDA should be considering when looking at patient experience data. The new language clarifies that patient experience data should not be limited to physical impacts of a disease or therapy, but they should also include psychosocial impacts. In addition, the data should not only consider other approved therapies, but they should also include investigational procedures currently in use. Read broadly, the language encourages FDA to consider a broad scope of patient experience data as part of the review process.

Real World Evidence in Regulatory Decision-Making. The use of Real World Evidence (RWE) in making regulatory decisions has been a focus of recent discussions among stakeholders and FDA. The 21st Century Cures Act defined (RWE) as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials," such as "ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities." In December 2016, several top FDA officials published an article in the New England Journal of Medicine acknowledging the benefits of real world evidence on patient care and postmarketing surveillance, but noting several concerns regarding the use of such study designs, which FDA concluded can "generate incorrect and unreliable conclusions." Although FDA has used RWE in some cases to evaluate the benefits and risks of already approved products, the use of RWE has been somewhat limited in terms of approving new uses and indications.

However, FDA has agreed in its PDUFA VI Commitment Letter to enhance the use of (RWE) in regulatory decision-making. Specifically, by the end of FY 2018, FDA will hold a public workshop for stakeholders to gather input on topics such as benefits of RWE to patients, regulators, and companies; challenges related to RWE availability, quality, and access; methodological approaches for the collection, analysis, and communication of RWE; and the context for using RWE for decision-making regarding effectiveness. In addition, FDA has committed to initiating or funding pilot studies and other projects intended to address the use of RWE by the end of FY 2019.

Under the 21st Century Cures Act, FDA was required to establish a program to evaluate the use of RWE in approving new supplemental indications and in fulfilling postmarketing commitments and requirements, and was required to publish draft guidance within five years of enactment. FDA confirmed in the PDUFA Commitment Letter that, by the end of FY 2021, FDA will publish draft guidance regarding how RWE can contribute to the assessment of safety and effectiveness in regulatory submissions.

Patient Voice in Drug Development. The PDUFA VI Commitment Letter also captures FDA's intent to utilize patient and caregiver input into drug development and regulatory decision-making. In an effort to translate increased patient advocacy and engagement in the drug regulatory process, FDA will integrate patient-focused methods by adding staff to review teams for applications where the sponsor intends to use patient-reported outcomes as part of the development program. FDA will also develop a series of guidance documents relating to:

- Methods and approaches to collecting meaningful patient and caregiver input.
- Processes and methodological approaches to identifying important aspects of the burden of disease and the burden of treatment.

— Developing measures for impacts, e.g., the burden of disease and treatment, to facilitate collection of patient input in clinical trials.
— Clinical outcome assessments, to supplement the 2009 Guidance to Industry on Patient Reported Outcome Measures.

In addition, FDA committed to creating and maintaining a repository of publicly available tools on its website, including a clinical outcome assessment compendium, patient-focused drug development meeting resources, and ongoing efforts on patient-focused drug development. FDA will also revise existing policies and procedures (MAPPs and SOPPs) to incorporate and increased patient focus in other FDA public meetings. By the end of FY 2019, FDA will conduct a public workshop to gather input from patient and caregiver communities and obtain insight on enhancing patient engagement in clinical trials.

IV. Orphan Drugs

Section 607 of FDARA amends Section 527 of the Federal Food, Drug, and Cosmetic Act, regarding orphan drugs, to impose a clinical superiority requirement as a prerequisite for orphan exclusivity. Under the new statutory provision, an orphan-designated drug will not qualify for orphan exclusivity if the "same drug" has previously been approved for the same rare disease or condition, unless the sponsor of the subsequent drug can show that its drug is clinically superior to the previously approved drug. This change to the orphan exclusivity provisions effectively reverses the holding *of Depomed, Inc. v. U.S. Dep't of Health & Human Servs.*, 66 F. Supp. 3d 217 (D.D.C. 2014). In *Depomed*, FDA's policy was held to be inconsistent with the plain language of the previous version of the exclusivity provision. The current amendment would permit FDA to return to its previous interpretation, at least on a prospective basis for drugs approved after the effective date of FDARA. Section 607 also directs FDA to make publicly available its clinical superiority decisions for approved products.

V. Pediatric Studies under PREA

Early Meeting on Pediatric Study Plan. Under the Pediatric Research Equity Act (PREA), as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), sponsors of NDAs, BLAs, and supplements for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration are required to conduct a pediatric assessment unless FDA grants the sponsor a waiver or deferral, based on statutory criteria. As part of the requirements, applicants must submit a pediatric plan outlining the pediatric studies the applicant plans to conduct. FDA has previously issued guidance regarding the content of and process for submitting initial pediatric study plans.

Section 503 of FDARA requires that FDA meet with sponsors early in the development process to discuss preparation of the initial pediatric study plan. If the meeting is requested by an applicant for a drug or biologic that is intended to treat a serious or life-threatening disease, the meeting must occur no later than the End-of-Phase 1 meeting, or within 30 calendar days of receipt of the request (whichever is later). The intent of the provision is to encourage early consultation for products intended for serious diseases. FDARA does not change the previous requirement for sponsors of other drugs or biologics to meet with FDA not later than 90 days after FDA's receipt of the initial pediatric study plan.

Pediatric Cancer Drug Development. Section 504 of FDARA amends PREA to authorize FDA to require pediatric studies for a drug or biological product that is (1) intended to treat adult cancers and (2) directed at a molecular target that FDA determines is substantially relevant to the growth or progression of a pediatric cancer (applies to original applications for a new active ingredient submitted three years after enactment). Within a year of enactment of FDARA, FDA is required to publish online and regularly update a list of molecular targets that may trigger the requirements, in addition to a list of targets for which pediatric study requirements will be automatically waived. Of note, this new requirement is applicable to orphan drugs, which are ordinarily exempt from PREA study requirements.

Action on Proposed Pediatric Study Request. Under the FDCA, certain applicants may obtain six months of exclusivity for submitting requested information on pediatric use of the product. Sponsors can obtain a Written Request from FDA by submitting a Proposed Pediatric Study Request (PPSR). A 1999 withdrawn guidance estimated that it could take FDA approximately 120 days after submission of a PPSR to issue a response.

Section 505 of FDARA requires FDA to review and act upon a submission of a PPSR or a proposed amendment to a written request for pediatric studies within 120 calendar days of submission. Other provisions include a requirement for FDA, within one year, to develop and implement a plan to achieve earlier submission of pediatric studies. The plan must include earlier discussions of PPSRs and written requests, earlier issuance of written requests for a pediatric study, and shorter timelines for completing studies pursuant to a written request.

VI. Facility Inspections

Expediting review of generic drug inspection responses. Section 806 of FDARA requires FDA to expedite its process for reviewing facility inspection responses, when an adequate response is necessary for a generic drug to be approved. Within six months of FDARA's enactment, FDA must implement a protocol to review Form FDA 483 responses within six months and address expedited facility re-inspection, as appropriate. The expedited review process is required when observed conditions must be remediated as a condition of a generic drug's approval and concerns related to FDA's inspectional observations are the only barrier to approval. The protocol is only required to apply if there are three or fewer approved ANDA referencing the same listed drug and fewer than six tentatively approved ANDAs or the drug is on FDA's drug shortage list.

Annual reports on inspections necessary for product approval or clearance. Section 902 of FDARA requires FDA to post on its website an annual report on FDA approval and clearance inspections. For inspections necessary for FDA approval/clearance, the report must include information on the median time it takes FDA to: begin an inspection once requested by FDA's review staff; issue a Form FDA 483 (483); issue a Warning Letter, import alert, or request for a regulatory meeting; and resolve regulatory or enforcement actions based on such inspections. The report also must state the number of times that, as a result of the issuance of a 483, FDA delayed approval of an application due to a withhold recommendation.

VII. Combination Products

The PDUFA 6 Goals Letter addresses, as part of FDA's goal to expedite drug development, advancing the development of combination products consisting of drugs, biologics, and/or devices. FDA is planning to more efficiently and consistently review combination product submissions, and

to meet this goal, the Agency has agreed to conduct reviews, develop internal and external guidances, and improve staff efficiencies.

FDA will conduct internal reviews of its own processes and contract with third parties to develop comprehensive assessments of agency processes. A report on the assessment will be published no later than the end of fiscal year 2020. To promote efficient, effective, and consistent product reviews, FDA will also establish Manuals of Policies and Procedures (MAPPs) and Standard Operating Policy and Procedures (SOPPs) that describe processes, responsibilities, and expectations for internal consultation. These documents will address human factor assessments, quality assessments and facility inspections, and patient-oriented labeling for drug-device and biologic-device combination products. The expected completion dates for these documents range from March-September, 2019. FDA will additionally publish new draft guidance or update older guidance by end of fiscal year 2022 for review staff and industry on bridging studies and patient-oriented labeling. FDA will develop additional staff capacity and capabilities in areas specific to combination products to allow for more efficient reviews and responses to submissions. By no later than December 31, 2018, FDA will make available on FDA's website key points of contact in OCP and the medical product centers for combination product review.

VIII. Expanded Access

FDARA Section 610 requires FDA to convene a public meeting, within 270 days of enactment, to discuss various ways in which participation in clinical trials, particularly regarding expanded access, can be improved. In addition, the General Accountability Office (GAO) is required to report to Congress on the expanded access program. FDA is also required to issue guidance on broadening eligibility criteria and increasing recruitment for clinical trials. Within one year of enactment, FDA must issue guidance or regulations to streamline the Institutional Review Board review of individual patient expanded access protocols. In addition, this section amends the provision enacted in 21st Century Cures Act requiring a manufacturer or distributor of an investigational drug to make public its policy on expanded access. The amendment will accelerate implementation of this provision for certain drugs by requiring that the expanded access policy must be made public the earlier of (1) the first initiation of a phase II or III study; or (2) 15 days after the drug receives a designation as breakthrough, fast-track, or regenerative advanced therapy. Under the 21st Century Cures Act, the manufacturer or distributor of an investigational drug was only required to make its expanded access policy publicly available at the first initiation of a phase II or III study.

IX. Tropical Disease Priority Review Vouchers

Section 611 narrows the tropical disease priority review voucher program, effective for applications submitted after September 30, 2017, by requiring the applicant to demonstrate that it conducted or sponsored at least one clinical investigation that is essential to the approval, and the applicant must attest that the study was not also submitted, prior to September 27, 2017, in support of licensure or marketing approval in India, Brazil, Thailand, or any country that is a member of the Pharmaceutical Inspection Convention or the Pharmaceutical Inspection Cooperation Scheme (PIC/S).

X. Drug Pricing

FDARA Section 609 provides the "sense of the Congress" that HHS "should commit to engaging" with Congress to take administrative actions and enact legislation to lower prescription drug costs

and reduce taxpayer burden. It calls for balancing innovation and affordability, and it emphasizes marketplace competition for generic drugs and biosimilars. This provision follows the announcement in May of FDA's Drug Competition Action Plan and subsequent implementation steps. While useful as a barometer of continued congressional interest in the issue, the language does not commit HHS or FDA to any active steps on drug pricing and appears unlikely to have any demonstrable policy effect.

XI. White House Proposal on 100% Fee Funded Regulatory Review

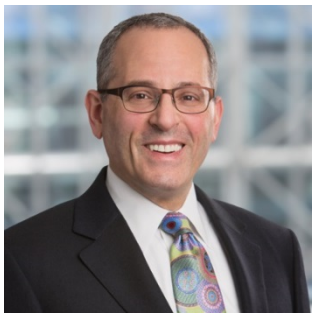
Finally, we note that FDARA does not align with the President's earlier budget proposal for fiscal year 2018, which called on Congress to expand medical product user fees by over $1 billion to replace the need for appropriated funds to cover pre-market review costs. In his letter to Patty Murray of May 15, 2017, HHS Secretary Tom Price urged that – consistent with the President's budget submission – FDA user fees be restructured to strip away the triggers that require a minimum threshold for appropriations. On July 12, the White House issued a Statement of Administration Policy on the user fee legislation, including the following: "The Administration urges the Congress to provide for 100 percent user fee funding with the reauthorized programs. In an era of renewed fiscal restraint, industries that benefit directly for FDA's work should pay for it." Neither the House- or Senate-passed bills included the requested user fee expansion.

* * * * *

If you have any questions about FDARA and how it may affect your business or organization, please contact one of the authors of this alert or the Hogan Lovells attorney with whom you regularly work.

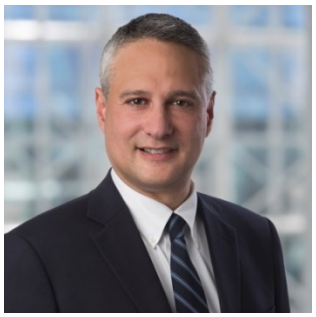
Contacts

Robert F. Church
Partner, Los Angeles
Tel +1 310 785 4646
robert.church@hoganlovells.com



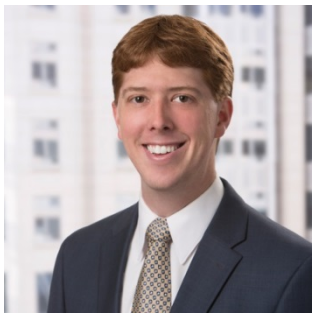
Michael N. Druckman
Partner, Washington, D.C.
Tel +1 202 637 5635
mike.druckman@hoganlovells.com

Heidi Forster Gertner
Partner, Washington, D.C.
Tel +1 202 637 5676
heidi.gertner@hoganlovells.com

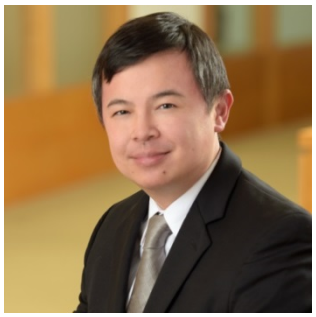


David Horowitz
Partner, Washington, D.C.
Tel +1 202 637 5403
david.horowitz@hoganlovells.com

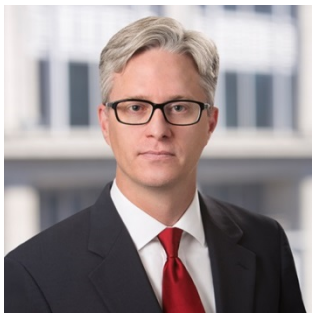
Gary L. Veron
Partner, Washington, D.C.
Tel +1 202 637 5480
gary.veron@hoganlovells.com



James S. Allred
Associate, Washington, D.C.
Tel +1 202 637 2721
james.allred@hoganlovells.com

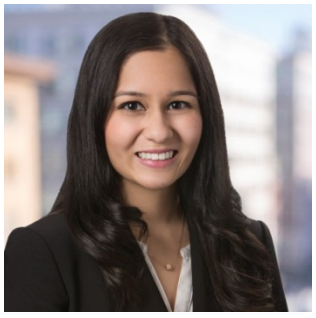


Bert Lao
Senior Associate, Los Angeles
Tel +1 310 785 4712
bert.lao@hoganlovells.com



George A. O'Brien
Senior Associate, Washington, D.C.
Tel +1 202 637 5497
george.obrien@hoganlovells.com

Katie Ruiz Medwid
Associate, Washington, D.C.
Tel +1 202 637 6462
katelyn.medwid@hoganlovells.com



Komal A. Karnik
Associate, Washington, D.C.
Tel +1 202 637 4883
komal.karnik@hoganlovells.com